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quest for grant of a patent

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Cardiff Road
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Your reference: 100662

Patent application number *(The Patent Office will fill in this part)*: 0205162.1 — 6 MAR 2002

Full name, address and postcode of the or of each applicant *(underline all surnames)*:
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S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)*: 7822448003

If the applicant is a corporate body, give the country/state of its incorporation: Sweden

Title of the invention: CHEMICAL COMPOUNDS

Name of your agent *(if you have one)*: Rachel M. Tinsley

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*:
AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
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Patents ADP number *(if you know it)*: 6921795002

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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Continuation sheets of this form	
Description	32
Claim*(s)*	
Abstract	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this applicat

Signature J.M. Marshall Date

Authorised Signatory 05/03/2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Joanne M. Marshall - 01625 - 516485

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CHEMICAL COMPOUNDS

The present invention relates to heterocyclic amide derivatives, pharmaceutically acceptable salts and *in vivo* hydrolysable esters thereof. These heterocyclic amides possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity and thus are potentially useful in methods of treatment of a warm-blooded animal such as man. The invention also relates to processes for the manufacture of said heterocyclic amide derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit glycogen phosphorylase activity in a warm-blooded animal such as man.

The liver is the major organ regulating glycaemia in the post-absorptive state. Additionally, although having a smaller role in the contribution to post-prandial blood glucose levels, the response of the liver to exogenous sources of plasma glucose is key to an ability to maintain euglycaemia. An increased hepatic glucose output (HGO) is considered to play an important role in maintaining the elevated fasting plasma glucose (FPG) levels seen in type 2 diabetics; particularly those with a FPG >140mg/dl (7.8mM). (Weyer et al, (1999), J Clin Invest 104: 787-794; Clore & Blackgard (1994), Diabetes 43: 256-262; De Fronzo, R. A., et al, (1992) Diabetes Care 15; 318 - 355; Reaven, G.M. (1995) Diabetologia 38; 3-13).

Since current oral, anti-diabetic therapies fail to bring FPG levels to within the normal, non-diabetic range and since raised FPG (and glycHbA1c) levels are risk factors for both macro- (Charles, M.A. et al (1996) Lancet 348, 1657-1658; Coutinho, M. et al (1999) Diabetes Care 22; 233-240; Shaw, J.E. et al (2000) Diabetes Care 23, 34-39) and micro-vascular disease (DCCT Research Group (1993) New. Eng. J. Med. 329; 977-986); the reduction and normalisation of elevated FPG levels remains a treatment goal in type 2 DM.

It has been estimated that, after an overnight fast, 74% of HGO was derived from glycogenolysis with the remainder derived from gluconeogenic precursors (Hellerstein et al (1997) Am J Physiol, 272: E163). Glycogen phosphorylase is a key enzyme in the generation by glycogenolysis of glucose-1-phosphate, and hence glucose in liver and also in other tissues such as muscle and neuronal tissue.

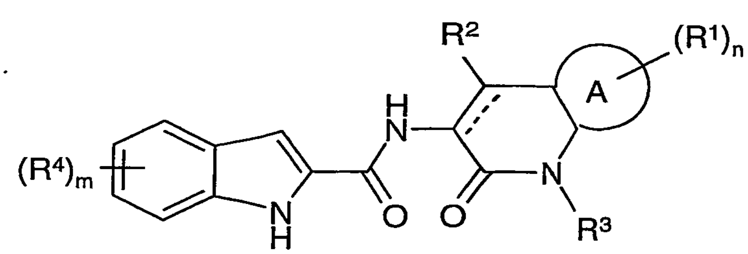
Liver glycogen phosphorylase a activity is elevated in diabetic animal models including the db/db mouse and the fa/fa rat (Aiston S et al (2000). Diabetalogia 43, 589-597).

Inhibition of hepatic glycogen phosphorylase with chloroindole inhibitors (CP9114[illegible] and CP320626) has been shown to reduce both glucagon stimulated glycogenolysis and glucose output in hepatocytes (Hoover et al (1998) J Med Chem 41, 2934-8; Martin et al (1998) PNAS 95, 1776-81). Additionally, plasma glucose concentration is reduced, in a dos related manner, db/db and ob/ob mice following treatment with these compounds.

Studies in conscious dogs with glucagon challenge in the absence and presence of another glycogen phosphorylase inhibitor, Bay K 3401, also show the potential utility of suc agents where there is elevated circulating levels of glucagon, as in both Type 1 and Type 2 diabetes. In the presence of Bay R 3401, hepatic glucose output and arterial plasma glucose following a glucagon challenge were reduced significantly (Shiota et al, (1997), Am J Physi 273: E868).

The heterocyclic amides of the present invention possess glycogen phosphorylase inhibitory activity and accordingly are expected to be of use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia and obesity, particularly type 2 diabetes.

According to one aspect of the present invention there is provided a compound of formula (1):



(1)

wherein:

---- is a single or double bond;

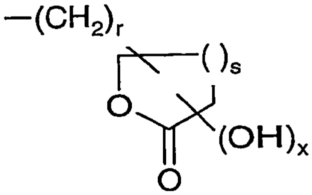
A is phenylene or heteroarylene;

m is 0, 1 or 2;

n is 0, 1 or 2;

wherein R^1 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, sulphamoyl, *N*-C_{1-4}alkylsulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, sulfino, sulfo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, hydroxyC_{1-4}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxy and

R^1 is of the formula A' or A":



(A') -$CH_2CH(OH)(CH_2)_uCO_2H$ (A")

wherein x is 0 or 1, r is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

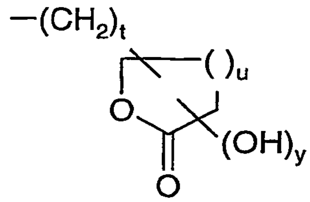
wherein R^4 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, sulphamoyl, *N*-C_{1-4}alkylsulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, sulfino, sulfo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, hydroxyC_{1-4}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoromethoxy;

R^2 is hydrogen, hydroxy or carboxy;

R^3 is selected from hydrogen, hydroxy, C_{1-4}alkanoyl, carbamoyl, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyano(C_{1-4})alkyl, 4-butanolidyl, 5-pentanolidyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, C_{1-4}alkyl [substituted by 1 or 2 R^8

groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)] and

groups of the formulae B and B':



(B) $-CH_2CH(OH)(CH_2)_uCO_2H$ (B')

wherein **y** is 0 or 1, **t** is 0, 1, 2 or 3 and **u** is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen);

{wherein R^8 is independently selected from hydroxy, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, 2,2-dimethyl-1,3-dioxolan-4-yl, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkoxy, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -N(OH)CHO, -COCOOR^9, $(R^9)(R^{10})$NCO-, $(R^9)(R^{10})NSO_2$-, -$COCH_2OR^{11}$, $(R^9)(R^{10})$N- and –COOR^9;

[wherein R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{5-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyano(C_{1-4})alkyl, 4-butanolidyl, 5-pentanolidyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl g, 1,1-dioxotetrahydrothiopyranyl, 2,2-dimethyl-1,3-dioxolan-4-yl and C_{1-4}alkyl substituted by R^{13};

(wherein R^{13} is selected from hydroxy, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -N(OH)CHO, $(R^{11})(R^{12})$NCO-, $(R^{11})(R^{12})NSO_2$-, -$COCH_2OR^{11}$, $(R^{11})(R^{12})$N- ;

{wherein R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, C_{1-4}alkylS(O)$_b$ (wherein b is 0, 1 or 2)}); and

R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, nitroso, cyano, isocyano, amino, N-C_{1-4}alkylamino, N,N-$(C_{1-4})_2$alkylamino, carbonyl, sulfo, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -N(OH)CHO, $(R^{11})(R^{12})$NCO-, $(R^{11})(R^{12})NSO_2$-, -$COCH_2OR^{11}$, $(R^{11})(R^{12})$N-;

wherein R^{11} and R^{12} are as defined above]};

provided that when R^1 is of the formula A' or A" then R^3 does not contain a group of the formula B or B' and when R^3 is of the formula B or B' then R^1 does not contain a group of the formula A' or A";

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In another aspect, the invention relates to compounds of formula **(1)** as hereinabove defined or to a pharmaceutically acceptable salt.

It is to be understood that, insofar as certain of the compounds of formula **(1)** defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses glycogen phosphorylase inhibition activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of the formula **(1)** or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has glycogen phosphorylase inhibition activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of the formula **(1)** and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have glycogen phosphorylase inhibition activity.

It is also to be understood that certain compounds of the formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess glycogen phosphorylase inhibition activity.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or wit sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates. In addition where the compounds of formula (1) are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic o organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

An *in vivo* hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy group is, for example. A pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-(C_{1-4})alkylcarbamoyl and *N*-(di-(C_{1-4})alkylaminoethyl)-*N*-(C_{1-4})alkylcarbamoyl (to give carbamates); di-(C_{1-4})alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C_{1-4})alkylaminomethyl and di-((C_{1-4})alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting in-vivo hyrolysable esters include, for example, $R^AC(O)O(C_{1-6})$alkyl-CO-, wherein R^A is for example, benzyloxy-(C_{1-4})alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(C_{1-4})piperazino-(C_{1-4})alkyl, piperazino-(C_{1-4})alkyl and morpholino-(C_1-C_4)alkyl.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "C_{1-4}alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. An analogous convention applies to other generic terms, for example "C_{2-4}alkenyl" includes vinyl, allyl and 1-propenyl and "C_{2-4}alkynyl" includes ethynyl, 1-propynyl and 2-propynyl.

The term "hydroxyC_{1-4}alkyl" includes hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl and hydroxybutyl. The term "hydroxyethyl" includes 1-hydroxyethyl and 2-hydroxyethyl. The term "hydroxypropyl" includes 1-hydroxypropyl, 2-hydroxypropyl and 3-hydroxypropyl and an analogous convention applies to terms such as hydroxybutyl. The term "dihydroxyC_{1-4}alkyl" includes dihydroxymethyl, dihydroxyethyl, dihydroxypropyl, dihydroxyisopropyl and dihydroxybutyl. The term "dihydroxyethyl" includes 1,1-dihydroxyethyl 2,2-dihydroxyethyl and 1,2-dihydroxyethyl. An analogous convention applies to terms such as dihydroxypropyl, dihydroxyisopropyl and dihydroxybutyl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

Examples of "C_{1-4}alkoxy" include methoxy, ethoxy, propoxy and isopropoxy. Examples of "C_{1-4}alkanoyl" include formyl, acetyl and propionyl. Examples of "C_{1-4}alkanoyloxy" are formyloxy, acetoxy and propionoxy. Examples of "*N*-(C_{1-4}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-4}alkyl)$_2$amino" include *N-N*-(methyl)$_2$amino, *N-N*-(ethyl)$_2$amino and *N*-ethyl-*N*-methylamino. Examples of "*N*-(C_{1-4}alkyl)carbamoyl" are methylcarbamoyl and ethylcarbamoyl. Examples of "*N,N*-(C_{1-4}alkyl)$_2$carbamoyl" are *N,N*-(methyl)$_2$carbamoyl, *N,N*-(ethyl)$_2$carbamoyl and *N*-methyl-*N*-ethylcarbamoyl. Examples of "*N*-(C_{1-4}alkyl)sulphamoyl are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N,N*-(C_{1-4}alkyl)$_2$sulphamoyl" are *N,N*-(methyl)$_2$sulphamoyl, *N,N*-(ethyl)$_2$sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl.

Examples of "C_{1-4}alkoxyC_{1-4}alkoxy" are methoxymethoxy, ethoxymethoxy, ethoxyethoxy and methoxyethoxy. Examples of "hydroxyC_{1-4}alkoxy" are hydroxyethoxy and hydroxypropoxy. Examples of "hydroxypropoxy" are 1-hydroxypropoxy, 2-hydroxypropoxy and 3-hydroxypropoxy.

Examples of "cyano(C_{1-4})alkyl" are cyanomethyl, cyanoethyl and cyanopropyl. Examples of "C_{5-7}cycloalkyl" are cyclopentyl, cyclohexyl and cycloheptyl. Examples of "C_{3-8}cycloalkyl" include "C_{5-7}cycloalkyl, cyclopropyl, cyclobutyl and cyclooctyl.

The term "aminoC_{1-4}alkyl" includes aminomethyl, aminoethyl, aminopropyl, aminoisopropyl and aminobutyl. The term "aminoethyl" includes 1-aminoethyl and 2-aminoethyl. The term "aminopropyl" includes 1-aminopropyl, 2-aminopropyl and 3-aminopropyl and an analogous convention applies to terms such as aminoethyl and aminobutyl.

Examples of "C_{1-4}alkylS(O)$_c$ (wherein c is 0 to 2)", "C_{1-4}alkylS(O)$_d$ (wherein d is 0 to 2)", "C_{1-4}alkylS(O)$_e$ (wherein e is 0 to 2)", and "C_{1-4}alkylS(O)$_f$ (wherein f is 0 to 2)" independently include methylthio, ethylthio, propylthio, methanesulphinyl, ethanesulphinyl, propanesulphinyl, mesyl, ethanesulphonyl, propanesulphonyl and isopropanesulphonyl.

Where optional substituents are chosen from "0, 1, 2 or 3" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chose from "0, 1 or 2" groups and "1 or 2" groups.

"Heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 5 to 7 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-and a ring sulphur atom may be optionally oxidised to form the S-oxide(s). Examples and suitable values of the term "heterocyclyl" are morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, dioxolanyl, thiadiazolyl, piperazinyl, isothiazolidinyl, triazolyl, tetrazolyl, pyrrolidinyl, 2-oxazolidinonyl, 5-isoxazolonyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-5-yl, tetrahydropyranyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, and oxadiazolyl. Preferably a "heterocyclyl" is morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl and 1,2,4-oxadiazolyl. More preferably heterocyclyl is oxazolyl, 1,2,4-oxadiazolyl, pyridyl, furyl, thienyl, morpholine, pyrazinyl and piperazinyl.

Examples of "(heterocyclyl)C_{1-4}alkyl" are morpholinomethyl, morpholinethyl, morpholinylmethyl, morpholinylethyl, piperidinomethyl, piperidinoethyl, piperidylmethyl, piperidylethyl, imidazolylmethyl, imidazolylethyl, oxazolylmethyl, oxazolylethyl 1,2,4-oxadiazolylmethyl, 1,2,4-oxadiazolylethyl, pyridylmethyl, pyridylethyl, furylmethyl, furylethyl, (thienyl)methyl, (thienyl)ethyl, pyrazinylmethyl, pyrazinylethyl, piperazinylmethyl and piperazinylethyl.

Examples of "aryl" are phenyl and naphthyl.

Examples of "aryl(C_{1-4})alkyl" are benzyl, 2-phenylethyl, naphthylmethyl and naphthylethyl.

"Heteroarylene" is a diradical of a heteroaryl group. A heteroaryl group is a partially saturated or unsaturated, monocyclic ring containing 5 to 7 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked; wherein a $-CH_2-$ group can optionally be replaced by a –C(O)- and a ring sulphur atom is optionally oxidised to form the S-oxide(s). Examples of heteroarylene are pyridylene, pyrimidinylene, pyrazinlyene, pyridazinylene, pyrrolylene, thienylene and furylene.

Preferred values of A, R^1, R^2, R^3, R^4, m and n are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one aspect of the invention A is phenylene.

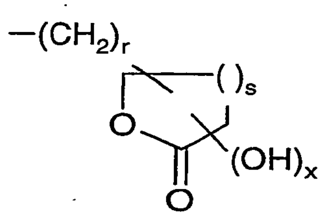
In another aspect of the invention A is heteroarylene.

Preferably A is selected from phenylene, pyridylene, pyrimidinylene, pyrrolylene, thienylene and furylene.

In one aspect of the invention n is 0 or 1.

Preferably n is 1.

In another aspect of the present invention R^1 is selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, C_{1-4}alkoxy and R^1 is of the formula A' or A":



(A') $-CH_2CH(OH)(CH_2)_uCO_2H$ (A")

wherein x is 0 or 1, r is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

Preferably R^1 is hydrogen or halo.

More preferably R^1 is hydrogen.

In one aspect of the invention q is 1.

In another aspect of the invention q is 2.

In one aspect of the invention $\overline{----}$ is a single bond.

In another aspect of the invention $\overline{----}$ is a double bond.

In one aspect of the invention R^2 is hydrogen.

In another aspect of the invention R^2 is carboxy.

In another aspect of the invention R^2 is hydroxy.

In one aspect on the invention R^3 is selected from hydrogen, hydroxy, C_{1-4}alkanoyl, carbamoyl, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyano(C_{1-4})alkyl, 4-butanolidyl, 5-pentanolidyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl and C_{1-4}alkyl [substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)];

{wherein R^8 is independently selected from hydroxy, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, 2,2-dimethyl-1,3-dioxolan-4-yl, 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -N(OH)CHO, -COCOOR^9, (R^9)(R^{10})NCO-, -COCH$_2$OR^{11}, (R^9)(R^{10})N- and –COOR^9 ;

[wherein R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), C_{5-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyano(C_{1-4})alkyl, 4-butanolidyl, 5-pentanolidyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, 2,2-dimethyl-1,3-dioxolan-4-yl and C_{1-4}alkyl substituted by R^{13} ;

(wherein R^{13} is selected from hydroxy, C_{1-4}alkoxy, 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl tetrahydrothienyl, C_{1-4}alkanoyl, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -N(OH)CHO, (R^{11})(R^{12})NCO-, (R^{11})(R^{12})NSO$_2$-, -COCH$_2$OR^{11}, (R^{11})(R^{12})N-;

{wherein R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, C_{1-4}alkylS(O)$_b$ (wherein b is 0, 1 or 2)}); and

R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, nitroso, cyano, isocyano, amino, *N*-C_{1-4}alkylamino, *N*,*N*-(C_{1-4})$_2$alkylamino, carbonyl, sulfo, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl,

C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -N(OH)CHO, $(R^{11})(R^{12})$NCO-, $(R^{11})(R^{12})NSO_2$-, -$COCH_2OR^{11}$, $(R^{11})(R^{12})$N- and wherein R^{11} and R^{12} are as defined above]};

In a further aspect of the invention R^3 is selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyanoC_{1-4}alkyl and C_{1-4}alkyl [substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)];

{wherein R^8 is independently selected from hydroxy, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, 2,2-dimethyl-1,3-dioxolan-4-yl, heterocyclyl, C_{1-4}alkoxy, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, $(R^9)(R^{10})$NCO-, -$COCOOR^9$, -$COOR^9$, $(R^9)(R^{10})$N-;

[wherein R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon) and C_{1-4}alkoxyC_{1-4}alkyl and wherein R^9 and R^{10} can together with the nitrogen to which they are attached form a 4- to 6-membered ring where the ring may be optionally substituted on carbon by 1 or 2 hydroxy groups or carboxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon)]}.

In yet a further aspect of the inventions R^3 is selected from hydrogen, hydroxyethyl, hydroxypropyl, 1,3-dihydroxyprop-2-yl, 3-hydroxy-2-hydroxymethylpropyl, 2,3-dihydroxypropyl, 2,2-dimethyl-1,3-dioxolan-4-ylmethyl, cyanomethyl, cyanoethyl, cyanopropyl, carbamoyl, carboxycarbonyl, methanoyl, ethanoyl, propanoyl, methoxymethyl, ethoxymethyl, methoxyethyl, ethoxymethyl, (2,3-dihydroxypyrrolidinyl)carbonylmethyl, (4-hydroxy)piperinocarbonylmethyl, *N,N*-(1,3-(2-carboxy)-propylene)carbamoylmethyl, 1,2,4-oxadiazolylmethyl, tetrazolylmethyl, imidazolylmethyl, pyrrolidinylmethyl, piperidylmethyl, tetrahydrofurylmethyl, tetrahydropyranylmethyl, (tetrahydrothiopyranyl)methyl, (tetrahydrothienyl)methyl, methanesulfinylethyl, methanesulfonylethyl, *N*-(1,3-dihydroxyisopropyl)carbamoylmethyl, 2-(methylamino)ethyl, 2-(dimethylamino)ethyl, 2-(ethylamino)ethyl, 2-(diethylamino)ethyl, 2-(*N*-methyl-*N*-ethylamino)ethyl, methoxycarbonylmethyl, carboxymethyl, carbomoylmethyl, (dimethylcarbamoyl)methyl, (methylcarbamoyl)methyl, (hydroxycabamoyl)methyl, (hydroxyethylcarbamoyl)methyl and (methoxyethylcarbamoyl)methyl and 2-(4-hydroxypiperidino)-2-oxoethyl.

In yet a further aspect of the invention R^3 is selected from hydrogen, carboxymethyl and methoxycarbonylmethyl.

In one aspect of the present invention m is 1 or 2.

In another aspect of the invention m is 1.

In one aspect of the present invention R^4 is selected from hydrogen, halo, cyano, hydroxy, fluoromethyl, difluoromethyl and trifluoromethyl.

In another aspect of the invention R^4 is hydrogen or halo.

Preferably R^4 is selected from hydrogen, chloro or bromo.

More preferably R^4 is chloro.

A preferred class of compound is of the formula (1) wherein;

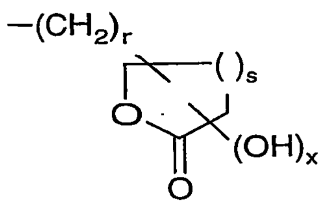
---- is a single bond;

A is phenylene;

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl and

R^1 is of the formula A' or A":



(A') $-CH_2CH(OH)(CH_2)_uCO_2H$ (A")

wherein x is 0 or 1, r is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^2 is hydrogen;

R^3 is selected from C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyanoC_{1-4}alkyl, and C_{1-4}alkyl [substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)];

{R^8 is independently selected from hydroxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkoxy, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -COCOOR^9, (R^9)(R^{10})NCO-, -COCH$_2$OR^{11}, (R^9)(R^{10})N-, –COOR^9 and 2,2-dimethyl-1,3-dioxolan-4-yl;

[R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon) and C_{1-4}alkyl substituted by C_{1-4}alkoxy and wherein R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from hydroxy or carboxy;

R^{11} is selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy and hydroxyC_{1-4}alkyl]};

m is 1 or 2;

R^4 is hydrogen or halo.

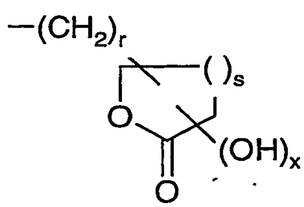
Another preferred class of compounds is of formula (1) wherein:

---- is a single bond;

A is phenylene;

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl and R^1 is of the formula A' or A":



(A') -CH$_2$CH(OH)(CH$_2$)$_u$CO$_2$H (A")

wherein x is 0 or 1, r is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^2 is hydrogen;

R^3 is selected from C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyanoC_{1-4}alkyl, and C_{1-4}alkyl [substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)]

{R^8 is independently selected from hydroxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkoxy, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -COCOOR^9, (R^9)(R^{10})NCO-, -$COCH_2OR^{11}$, (R^9)(R^{10})N-, –COOR^9 and 2,2-dimethyl-1,3-dioxolan-4-yl;

[R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon) and C_{1-4}alkyl substituted by C_{1-4}alkoxy and wherein R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from hydroxy or carboxy;

R^{11} is selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy and hydroxyC_{1-4}alkyl]};

m is 1 or 2;

R^4 is hydrogen or halo.

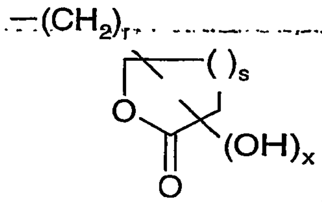
Another preferred class of compound is of the formula (1) wherein:

$\overline{----}$ is a single bond;

A is phenylene;

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl and R^1 is of the formula A' or A":



(A') $-CH_2CH(OH)(CH_2)_uCO_2H$ (A'')

wherein x is 0 or 1, r is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^2 is hydrogen;

R^3 is selected from C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyanoC_{1-4}alkyl, and C_{1-4}alkyl [substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)];

{R^8 is independently selected from hydroxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkoxy, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, $-COCOOR^9$, $(R^9)(R^{10})NCO-$, $-COCH_2OR^{11}$, $(R^9)(R^{10})N-$, $-COOR^9$ and 2,2-dimethyl-1,3-dioxolan-4-yl;

R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon) and C_{1-4}alkyl substituted by C_{1-4}alkoxy and wherein R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from hydroxy or carboxy;

R^{11} is selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy and hydroxyC_{1-4}alkyl]};

m is 1 or 2;

R^4 is hydrogen or halo.

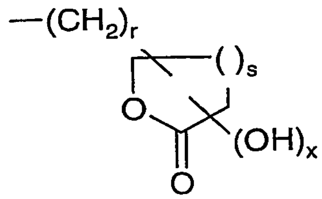
A further preferred class of compound is of the formula (1) wherein;

$\overline{}$ is a single bond;

A is phenylene;

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl and R^1 is of the formula A' or A":



(A') -$CH_2CH(OH)(CH_2)_uCO_2H$ (A")

wherein x is 0 or 1, r is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^2 is hydrogen;

R^3 is selected from C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon);

m is 1 or 2;

R^4 is hydrogen or halo.

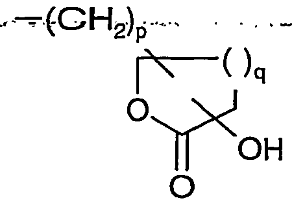
A further preferred class of compound is of the formula (1) wherein;

$\overline{- - -}$ is a single bond;

A is phenylene;

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl and



where p is 0, 1, 2 or 3 and q is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^2 is hydrogen;

R^3 is selected from cyanoC_{1-4}alkyl, and C_{1-4}alkyl substituted by R^8 ;

R^8 is selected from $(R^9)(R^{10})$NCO-, $(R^9)(R^{10})$N-, and –COOR^9 ;

R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon) and C_{1-4}alkyl substituted by C_{1-4}alkoxy and wherein R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from hydroxy or carboxy;

m is 1 or 2;

R^4 is hydrogen or halo.

A further preferred class of compound is of the formula (1) wherein;

$\overline{----}$ is a single bond;

A is phenylene;

n is 1 or 2;

R^1 is hydrogen;

R^2 is hydrogen;

R^3 is hydrogen, carboxymethyl or methoxycarbonylmethyl;

m is 1 or 2;

R^4 is hydrogen or halo.

A further preferred class of compound is of the formula (1) wherein;

$\overline{\text{----}}$ is a single bond;

A is phenylene;

n is 1 or 2;

R^1 is hydrogen;

R^2 is hydrogen;

R^3 is hydrogen, carboxymethyl or methoxycarbonylmethyl;

m is 1;

R^4 is chloro.

Another class of compounds is of the formula (1) wherein

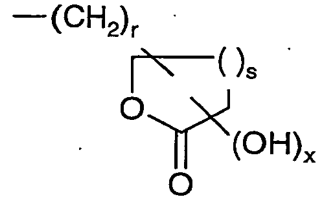
$\overline{\text{----}}$ is a double bond;

A is phenylene;

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl and

R^1 is of the formula A' or A'':



(A') $-CH_2CH(OH)(CH_2)_uCO_2H$ (A'')

wherein x is 0 or 1, r is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^2 is carboxy;

R^3 is selected from hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups, provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyanoC_{1-4}alkyl, and C_{1-4}alkyl substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon);

{R^8 is independently selected from hydroxy, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkoxy, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -$COCOOR^9$, $(R^9)(R^{10})NCO$-, -$COCH_2OR^{11}$, $(R^9)(R^{10})N$-, –$COOR^9$ and 2,2-dimethyl-1,3-dioxolan-4-yl;

[R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon) and C_{1-4}alkyl substituted by C_{1-4}alkoxy and wherein R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from hydroxy or carboxy;

R^{11} is selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy and hydroxyC_{1-4}alkyl]};

m is 1 or 2;

R^4 is hydrogen or halo.

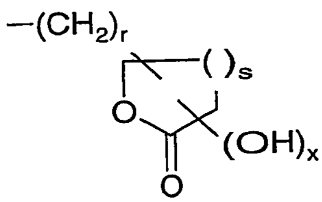
A further class of compound is of formula (1) wherein:

$\overline{----}$ is a single bond;

A is pyridylene;

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl and R^1 is of the formula A' or A":



(A') -$CH_2CH(OH)(CH_2)_uCO_2H$ (A")

wherein x is 0 or 1, r is 0, 1, 2 or 3 and s is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^2 is hydrogen;

R^3 is selected from hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon), cyanoC_{1-4}alkyl, and C_{1-4}alkyl [substituted by 1 or 2 R^8 groups (provided that when there are 2 R^8 groups they are not substituents on the same carbon)];

{R^8 is independently selected from hydroxy, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkoxy, C_{1-4}alkanesulfinyl, C_{1-4}alkanesulfonyl, -$COCOOR^9$, $(R^9)(R^{10})NCO$-, -$COCH_2OR^{11}$, $(R^9)(R^{10})N$-, –$COOR^9$ and 2,2-dimethyl-1,3-dioxolan-4-yl;

[R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon) and C_{1-4}alkyl substituted by C_{1-4}alkoxy and wherein R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from hydroxy or carboxy;

R^{11} is selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy and hydroxyC_{1-4}alkyl]};

m is 1 or 2;

R^4 is hydrogen or halo.

In another aspect of the invention, preferred compounds of the invention are any one of:

methyl 2-[3-(5-chloro-1*H*-indol-2-ylcarbonylamino)-2-oxo-3,4-dihydroquinolin-1(2*H*)-yl]acetate;

2-[3-(5-chloro-1*H*-indol-2-ylcarbonylamino)-2-oxo-3,4-dihydroquinolin-1(2*H*)-yl]acetic acid;

2-[*N*-(2-oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl]-5-chloro-1*H*-indole;

2-{*N*-[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydroquinol-3-yl]carbamoyl}-5-chloro-1*H*-indole;

5-Chloro-N-[1-(2,3-dihydroxypropyl)-1,2,3,4-tetrahydro-2-oxo-3-quinolinyl]-1H-indole-2-carboxamide;

3-[[(5-Chloro-1H-indol-2-yl)carbonyl]amino]-3,4-dihydro-2-oxo-1(2H)-quinolineacetamide;

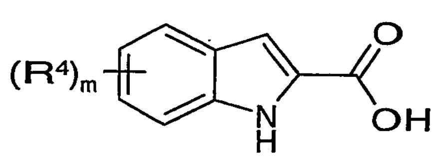
5-Chloro-N-[1,2,3,4-tetrahydro-1-(2-hydroxyethyl)-2-oxo-3-quinolinyl]- 1H-indole-2-carboxamide;

3-[[(5-Chloro-1H-indol-2-yl)carbonyl]amino]-3,4-dihydro-2-oxo-1(2H)-quinolineacetic acid;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

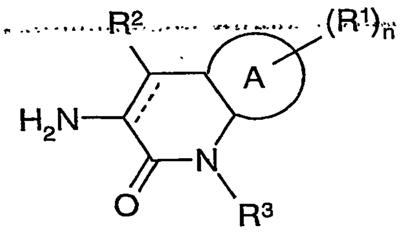
Another aspect of the present invention provides a process for preparing a compound of formula (1) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein A, R^1, R^2, R^3, R^4, m, n and --- are, unless otherwise specified, as defined in formula (**1**)) comprises of:

a) reacting an acid of the formula (**2**):



(**2**)

or an activated derivative thereof; with an amine of formula (**3**):



(3)

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

Specific reaction conditions for the above reaction are as follows.

Process a) Acids of formula (2) and amines of formula (3) may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as 1-hydroxybenzotriazole, dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

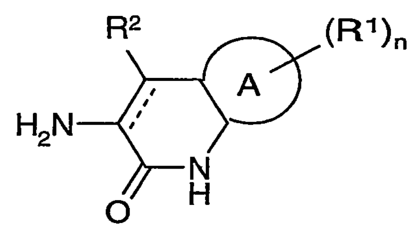
Where R^3 of formula (1) contains an ester group, the conversion of a compound of the formula (1) into another compound of the formula (1) may involve hydrolysis of the ester group. The reaction of this type is well known in the art.

Where R^3 of formula (1) contains –COOH group, the conversion of a compound of the formula (1) into another compound of the formula (1) may involve reduction of this group

using reducing agents such as lithium borohydride, sodium borohydride etc.. The conversion may also involve the coupling of this -COOH group with ammonia or a substituted amine in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide.

The acids of formula (2) are commercially available or they are know compounds or they are prepared by processes known in the art.

Compounds of formula (3) may be prepared by reacting an amine of formula (4)



(4)

with R^3-L where L is a suitable leaving group (for example chloro, bromo or iodo) in the presence of a base such as sodium hydride in a suitable solvent.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic

hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkanesulphinyl or alkanesulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Certain intermediates in the preparation of a compound of the formula (1) are novel and form another aspect of the invention.

As stated hereinbefore the compounds defined in the present invention possesses glycogen phosphorylase inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Assay

The activity of the compounds is determined by measuring the inhibitory effect of the compounds in the direction of glycogen synthesis, the conversion of glucose-1-phosphate into glycogen with the release of inorganic phosphate, as described in EP 0 846 464 A2. The reactions were in 96well microplate format in a volume of 100μl. The change in optical density due to inorganic phosphate formation was measured at 620nM in a Labsystems iEMS Reader MF by the general method of (Nordlie R.C and Arion W.J, Methods of Enzymology, 1966, 619-625). The reaction is in 50mM HEPES, 2.5mM $MgCl_2$, 2.25mM ethylene glycol-bis(b-aminoethyl ether) *N,N,N',N'*-tetraacetic acid, 100mM KCl, 2mM D-(+)-glucose pH7.2, containing 0.5mM dithiothreitol, the assay buffer solution, with 0.1mg type III glycogen, 0.15ug glycogen phosphorylase *a* (GP*a*) from rabbit muscle and 0.5mM glucose-1-phosphate. GP*a* is pre-incubated in the assay buffer solution with the type III glycogen at 2.5 mg ml^{-1} for 30 minutes. 40μl of the enzyme solution is added to 25μl assay buffer solution and the reaction started with the addition of 25μl 2mM glucose-1-phosphate. Compounds to be tested are prepared in 10μl 10% DMSO in assay buffer solution, with final concentration of 1% DMSO in the assay. The non-inhibited activity of GP*a* is measured in the presence of 10μl 10% DMSO in assay buffer solution and maximum inhibition measured in the presence of 30μM CP320626 (Hoover et al (1998) J Med Chem 41, 2934-8; Martin et al (1998) PNAS 95, 1776-81). The reaction is stopped after 30min with the addition of 50μl acidic ammonium

molybdate solution, 12ug ml^{-1} in 3.48% H_2SO_4 with 1% sodium lauryl sulphate and 10ug ml^{-1} ascorbic acid. After 30 minutes at room temperature the absorbency at 620nm is measured.

The assay is performed with a range of test concentrations of inhibitor to determine an IC_{50}, a concentration predicted to inhibit the enzyme reaction by 50%.

Activity is calculated as follows:-

% inhibition = (1 - (compound OD620 - fully inhibited OD620)/ (non-inhibited rate OD620 - fully inhibited OD620)) * 100.

OD620 = optical density at 620nM.

Typical IC_{50} values for compounds of the invention when tested in the above assay are in the range 100μM to 1nM. For example IC_{50} of example 2 is 0.55μM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (1) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of producing a glycogen phosphorylase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the

host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

In addition to their use in therapeutic medicine, the compounds of formula (1) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C and under an atmosphere of an inert gas such as argon;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a Bond Elut column is referred to, this means a column containing 10 g or 20 g or 50 g of silica of 40 micron particle size, the silica being contained in a 60 ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI"; "Mega Bond Elut" is a trademark; where a Biotage cartridge is referred to this means a cartridge containing KP-SIL™ silica, 60μ, particle size 32-63mM, supplied by Biotage, a division of Dyax Corp., 1500 Avon Street Extended, Charlottesville, VA 22902, USA;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) where given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-δ_6) as solvent unless otherwise indicated, other solvents (where indicated in the text) include deuterated chloroform $CDCl_3$;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

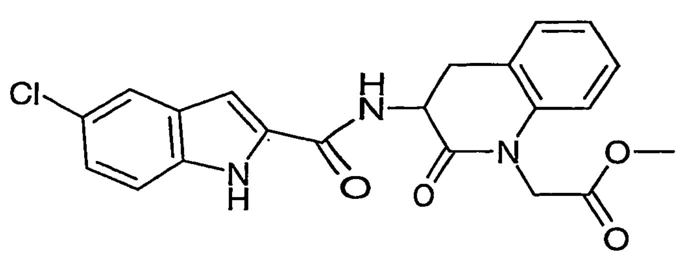
(ix) solvent ratios are given in volume : volume (v/v) terms;

(x) The following abbreviations are used:

EtOAc	ethyl acetate;
DCM	dichloromethane;
HOBT	1-hydroxybenzotriazole;
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride;
Et_2O	diethyl ether;
THF	tetrahydrofuran;
DMF	*N*, *N*-dimethylformamide;

Example 1

Methyl 2-[3-(5-chloro-1*H*-indol-2-ylcarbonylamino)-2-oxo-3,4-dihydroquinolin-1(2*H*)-yl]acetate



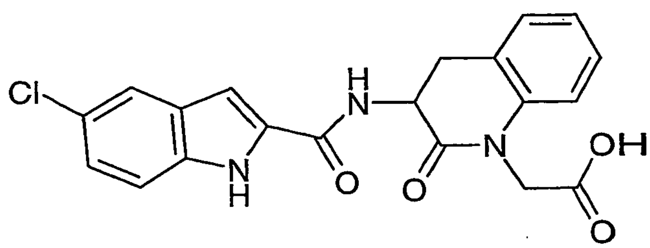
5-Chloro-1*H*-indole-2-carboxylic acid (493 mg, 2.52 mmol), HOBt (340 mg, 2.52 mmol), DCM (100 mL) and finally EDCI (483 mg, 2.52 mmol) were added to methyl 2-(3-amino-2-oxo-3,4-dihydroquinolin-1(2*H*)-yl)acetate (**Method 1**; 590 mg, 2.52 mmol) and the reaction was stirred for 18 h. The reaction was then diluted with water (50 mL) and stirred vigorously for 30 min. The resultant precipitate was filtered and washed with Et_2O (2 x 20

mL). After filtration the resultant solid was then triturated with refluxing Et_2O (25 mL) and after cooling the title compound (608 mg, 59%) was collected again by filtration as a white solid.

^{1}H NMR 3.11 (dd, 1H), 3.25 (app. t, 1H), 3.69 (s, 3H), 4.67 (d, 1H), 4.83 (m, 2H), 7.09 (m, 2H), 7.23 (m, 2H), 7.32 (m, 2H), 7.47 (d, 1H), 7.76 (s, 1H), 8.92 (d, 1H), 11.83 (s, 1H); MS m/z MNa^+ 434, 436.

Example 2

2-[3-(5-Chloro-1*H*-indol-2-ylcarbonylamino)-2-oxo-3,4-dihydroquinolin-1(2*H*)-yl]acetic acid:

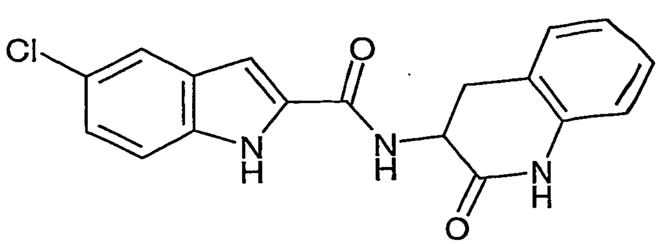


LiOH (91.5 g, 2.18 mmol) in H_2O (2 mL) was added to a stirring solution of methyl 2-[3-(5-chloro-1*H*-indol-2-ylcarbonylamino)-2-oxo-3,4-dihydroquinolin-1(2*H*)-yl]acetate (**Example 1**; 557 mg, 1.09 mmol) in THF (11 mL) and the reaction was stirred for 3 h. The reaction was quenched by addition of 1M aqueous HCl (40 mL) and EtOAc (60 mL) and the organic layer was dried ($MgSO_4$), filtered and evaporated. The resultant white foam was triturated with hot Et_2O (20 mL) cooled, filtered, dried and collected by filtration to afford the title compound (500 mg, 92%) as a white solid.

^{1}H NMR 3.08 (dd, 1H), 3.25 (app. t, 1H), 4.53 (d, 1H), 4.77 (m, 2H), 7.06 (m, 2H), 7.24 (m, 4H), 7.45 (d, 1H), 7.74 (s, 1H), 8.90 (d, 1H), 11.83 (s, 1H); MS m/z MH^+ 398, 400.

Example 3

2-[*N*-(2-Oxo-1,2,3,4-tetrahydroquinol-3-yl)carbamoyl)-5-chloro-1*H*-indole



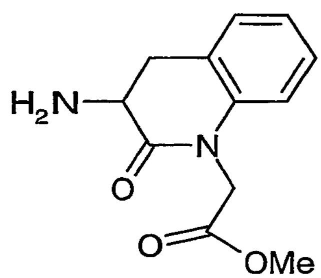
5-Chloroindole-2-carboxylic acid (196mg, 1mmol) was dissolved in DMF (5 mL) containing 3-amino-3,4-dihydroquinolin-2(1*H*)-one hydrochloride (*J. Med. Chem. 28*, **1985**,

1511-16; 162mg, 1mmol), EDCI (192 mg, 1 mmol) and HOBt (135 mg, 1 mmol). The mixture was stirred at ambient temperature for approximately 18 h before being partitioned between water and EtOAc. The organics were washed with water, saturated aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$; then filtered and evaporated to afford the title compound (212 mg, 66%) as an amorphous white solid.

^1H NMR 3.13 (m, 2H), 4.77 (m, 1H), 6.92 (d, 1H), 6.96 (t, 1H), 7.21 (m, 4H), 7.47 (d, 1H), 7.76 (d, 1H), 8.80 (d, 1H), 10.38 (s, 1H), 11.84 (s, 1H); MS m/z MH^+ 340, 342.

Method 1

Methyl 2-[3-amino-2-oxo-3,4-dihydroquinolin-1(2*H*)-yl]acetate



Sodium hydride (60% in oil, 2.52 g, 63.0 mmol) was added to 3-amino-3,4-dihydroquinolin-2(1*H*)-one hydrochloride (*J. Med. Chem. 28*, **1985**, 1511-16; 5.0 g, 25.2 mmol), in anhydrous DMF (100 mL) at 0 °C over a period of 5 min keeping the internal temperature at <10 °C. The reaction was stirred for a further 30 min before addition of methyl bromoacetate (2.85 mL, 30.2 mmol), then stirred for a further 60 min. The reaction was quenched by addition of 1M aqueous HCl (5 mL) and the volatiles were removed by evaporation. The residue was dissolved in DCM (250 mL) and washed with sat. aqueous $NaHCO_3$ (100 mL) and the organic layer was dried ($MgSO_4$); filtered and evaporated to yield the title compound (5.89 g, 100%) as yellow paste which was used in the next reaction without further purification.

^1H NMR 2.21 (br. s, 2H), 2.78 (d, 1H), 2.97 (dd, 1H), 3.47 (dd, 1H), 3.67 (s, 3H), 4.55 (d, 1H), 4.78 (d, 1H), 6.96 (m, 2H), 7.23 (m, 2H); MS m/z MH^+ 235.